Direct cell reprogramming as a new emerging strategy in cardiac regeneration

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99-O-1 Direct cell reprogramming as a new emerging strategy in cardiac regeneration

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Myocardial infarction (MI) is the current leading cause of mortality in the industrialised world. It is due to the irreversible death of billions of cardiomyocytes, secondary to a condition of ischemia. This leads to the formation of a stiff fibrotic tissue, mainly populated by cardiac fibroblasts (CFs). Currently, the only available therapy addressing the irreversible loss of functional cardiomyocytes is heart transplantation. Different tissue engineering approaches and cell therapies are under investigation, aimed at recovering myocardial contractility. Main issues in these strategies are the poor grafting and survival ability of implanted cells as well as the limited endogenous regenerative potential of adult heart.

A new strategy is now emerging based on direct reprogramming of CFs into induced cardiomyocytes (iCMs) using transcriptional factors and/or microRNAs (miRNAs) (miR-combo) [2-4]. Proof of concepts results of *in vitro* and *in vivo* conversion of mouse CFs into iCMs have been published and *in vitro* direct reprogramming of human CFs has also been reported [1-3]. However, such strategy is still an immature approach: reprogramming efficiency is low and partially reprogrammed non-beating cardiomyocytes have been generally obtained. Recently, *in vitro* direct reprogramming efficiency of mouse CFs cultured in 3D fibrin hydrogels using miR-combo has resulted significantly increased compared to 2D culture systems [4].

Based on these preliminary results, in this work we studied the miR-combo mediated reprogramming efficiency of human dermal and cardiac fibroblasts cultured on hydrogel matrices, including fibrin, fibrin/laminin, fibrin/fibronectin and fibrin/cardiac biomatrix [5], by analysing cell morphology, cell viability, change in gene expression (PCR analysis) and presence of markers of trans-differentiation by immunohistochemistry. The 3D biomimetic hydrogels were able to increase reprogramming efficiency respect to 2D culture environment, both at a genetic and protein level, with an enhancement in the expression of cardiac genes and cardiac proteins such as cardiac troponin I and alpha sarcomeric actinin.

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